Complete Summary

GUIDELINE TITLE

Management and diagnostic guidelines for urticaria and angio-oedema.

BIBLIOGRAPHIC SOURCE(S)

Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. Br J Dermatol 2001 Apr;144(4):708-14. [27 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Urticaria and angio-oedema

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Dermatology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence based recommendations for the treatment of patients with urticaria and angio-oedema

TARGET POPULATION

Patients with urticaria and angio-oedema

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Clinical signs and symptoms
2. Relevant laboratory tests
    - Skin-prick testing of potential allergens
    - Radioallergosorbent tests (RAST)
    - Full blood count
    - White cell differential
    - Erythrocyte sedimentation rate
    - Thyroid autoantibodies
    - Thyroid function tests
    - C4 component of complement (for C1 esterase deficiency)
    - Biopsy

Treatment/Management

1. Avoidance of aggravating factors/drugs
2. Patient education
3. Antipruritic lotion
4. Antihistamines
    - Non-sedating H1 antagonists (fexofenadine, loratadine, mizolastine, acrivastine, cetirizine)
    - Sedating antihistamines (chlorpheniramine, hydroxyzine)
    - H2 antagonists
5. Corticosteroids
    - Prednisolone (oral)
    - Intravenous hydrocortisone
6. Epinephrine (adrenaline)
7. Immunosuppressive therapies
    - Plasmapheresis
    - Intravenous immunoglobulin
    - Cyclosporin A
8. Pseudoallergen diet
9. Thyroxine
10. C1 Esterase Inhibitor Prophylaxis/Emergency
    - Stanozolol

- Danazol
- Tranexamic acid
- C1 inhibitor concentrate
- Fresh frozen plasma

Interventions Considered But Not Recommended

Oral sodium cromoglycate, topical steroids, psoralen photochemotherapy, ultraviolet B phototherapy and relaxation therapies

MAJOR OUTCOMES CONSIDERED

- Symptom improvement
- Side effects of treatment
- Incidence of recurrence
- Severity of recurrence
- Prognosis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

I: Evidence obtained from at least one properly designed, randomized controlled trial

II-i: Evidence obtained from well designed controlled trials without randomization

II-ii: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

IV: Evidence inadequate owing to problems of methodology (e.g., sample size, or length or comprehensiveness of follow-up or conflicts of evidence)

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendation Grades

A. There is good evidence to support the use of the procedure.
B. There is fair evidence to support the use of the procedure.
C. There is poor evidence to support the use of the procedure.
D. There is fair evidence to support the rejection of the use of the procedure.
E. There is good evidence to support the rejection of the use of the procedure.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines are edited by the Therapy Guidelines and Audit Sub-committee (TGA) and subsequently returned to the task force for revision. The approved draft version is published in the quarterly British Association of Dermatologists (BAD) newsletter, and all BAD members are given the opportunity to respond, positively or negatively, but hopefully helpfully, within three months of publication. Finalised guidelines are approved by the TGA and the Executive Committee of the BAD and finally published in the British Journal of Dermatology.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (I-IV) and strength of recommendation ratings (A-D) are defined at the end of the "Major Recommendations" field.

Clinical Classification

It is usually possible to classify urticaria on the clinical presentation supported, where appropriate, by challenge tests and skin biopsy (see Table 1 in the original guideline document). The duration of individual weals can be helpful: they typically last from 2 to 24 hours in ordinary urticaria and up to 2 hours in contact urticaria. The weals of physical urticaria are gone within an hour except those in delayed pressure urticaria, which take longer to develop and to fade. C1 esterase inhibitor deficiency should be excluded if recurrent angio-oedema presents without weals. Patients with C1 esterase inhibitor deficiency may have a family history of this disorder or may present with abdominal pain. Contact urticaria may present with symptoms ranging from burning and stinging at the site of skin contact to localized wealing and, rarely, generalized urticaria following percutaneous absorption of the eliciting substance. The lesions of urticarial vasculitis usually persist for days but may look indistinguishable from ordinary urticaria, which is why this presentation of vasculitis is usually included in classifications of urticaria. Other urticarial rashes, such as drug eruptions, are not urticaria.

Appropriate Investigations

The diagnosis of urticaria is primarily clinical. Any investigations should be guided by the history and should not be performed in all patients. Relevant clinical and laboratory tests for the different presentations of urticaria are summarized in Table 3 in the original guideline document.

Acute or Episodic Ordinary Urticaria

No investigations are required except where suggested by the history. Immunoglobulin E (IgE)-mediated reactions to environmental allergens (such as latex, nuts, or fish) as a cause of acute urticaria and contact urticaria can be confirmed by skin-prick testing (where there are facilities) and radioallergosorbent tests (RAST) on blood. Results of both have to be interpreted in the clinical context.

Chronic Ordinary Urticaria

No investigations are required for the majority of patients with mild disease responding to antihistamines. A useful screening profile for non-responders with more severe disease could include a full blood count and white cell differential (for instance, to detect the eosinophilia of bowel helminth infections), and erythrocyte sedimentation rate (usually normal in chronic idiopathic urticaria [CIU] but may be raised in urticarial vasculitis). Thyroid autoantibodies should be considered and thyroid function tests performed if thyroid dysfunction is likely. There is currently no routine laboratory test for histamine-releasing autoantibodies but intradermal injection of autologous serum (the autologous serum skin test) offers a reasonably sensitive and specific screening test in centres with experience.

Physical Urticarias

Physical urticarias may occur alone or coexist with ordinary urticaria. International standards for the diagnosis of physical urticarias and definitions of challenge testing have been proposed.

Urticarial Vasculitis

Lesional skin biopsy is essential to confirm the presence of small-vessel vasculitis histologically (endothelial cell damage, leukocytoclasia, and fibrin deposition are cardinal features). Patients with urticarial vasculitis need a full vasculitis screen, including serum complement assays.

Angio-oedema without Weals

Hereditary and acquired C1 esterase inhibitor deficiency should be screened by assaying serum C4, which is rapid and inexpensive with very high sensitivity but low specificity. If low, C1 esterase inhibitor deficiency can be confirmed by quantitative and functional C1 esterase inhibitor assays.

Interventions

General Measures

Non-specific aggravating factors, such as overheating, stress, alcohol, and drugs with the potential to worsen urticaria (e.g., aspirin and codeine) should be minimized.

In general, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in aspirin-sensitive urticaria patients. Angiotensin-converting enzyme (ACE) inhibitors should be used with caution in patients with concurrent angio-oedema or urticaria not caused by the drug. Cooling antipruritic lotions, such as 1% menthol in aqueous cream and calamine lotion can be soothing (Strength of Recommendation A, Quality of Evidence III). Clearly written information sheets, such as the British Association of Dermatologists' publication on Urticaria and Angio-oedema, can be very helpful to patients. It is important to explain to the patient that a cause of the condition is unlikely to be found.

Antihistamines

The efficacy and safety of antihistamines in urticaria is undisputed although not all patients respond and some, very occasionally, become worse. Four non-sedating H1 receptor antagonists are currently licensed for urticaria in the UK. Fexofenadine, loratadine, and mizolastine are taken once daily. Acrivastine is taken three times a day in view of its short half-life (1.5 hours). Cetirizine (the active metabolite of hydroxyzine) is minimally sedating. Mizolastine is contraindicated in heart failure and when there is prolongation of the Q-T interval. It should be avoided with drugs which inhibit hepatic metabolism via cytochrome P450 (including macrolide antibiotics and imidazole antifungals) and with drugs that have potential arrhythmic properties (including tricyclic antidepressants, such as doxepin).

All patients should be offered the choice of at least two non-sedating H1 antagonists because responses and tolerance vary between individuals (A). It is common practice to increase the dose above the manufacturer's licensed recommendation when the potential benefits are considered to outweigh any risks (III).

Adjustments to the timing of medication can be helpful to ensure that the highest drug levels are obtained when urticaria is expected to be most active.

Addition of a sedating antihistamine (e.g., chlorpheniramine 4 to 12 mg, hydroxyzine 10 to 50 mg) at night to a non-sedating antihistamine may help patients sleep better, although they probably add little to existing H1 receptor blockade. The addition of an H2 antagonist, on the other hand, may give better control of urticaria than H1 antagonists alone (I, B) although a benefit is not always seen.

Antihistamines in Pregnancy

If possible, it is best to avoid all antihistamines in pregnancy, especially during the first trimester, although none have been shown to be teratogenic in humans. Current manufacturers' Data Sheets recommend that cetirizine, loratadine, and mizolastine should be avoided in pregnancy and breast feeding. Chlorpheniramine is often chosen by clinicians when antihistamine therapy is necessary, because of its long safety record.

Antihistamines in Childhood

None of the antihistamines are contraindicated in children over 12 years. As dosing and age restrictions for individual products vary widely in younger children, it is recommended that the relevant Data Sheets are consulted before prescribing.

Mast Cell Stabilizing Drugs

Drugs with mast-cell stabilizing properties are not licensed for urticaria. Ketotifen has been used for its antihistaminic properties but is sedating. Oral sodium cromoglycate is not effective for urticaria. Nifedipine has been shown to reduce pruritus and wealing in chronic idiopathic urticaria (CIU) (I, B), presumably by modifying calcium influx into cutaneous mast cells, but the overall clinical benefit is often disappointing.

Corticosteroids

Oral corticosteroids may shorten the duration of acute urticaria (e.g., prednisolone 50 mg/day for 3 days in adults). Intravenous hydrocortisone is a useful adjunct for severe laryngeal oedema and anaphylaxis when given as a stat dose, although its action is delayed. Short tapering courses of oral steroids over 3 to 4 weeks may be necessary for urticarial vasculitis and severe delayed pressure urticaria (III) but long-term oral corticosteroids should not be used in chronic urticaria (A) except in very selected cases under regular specialist supervision.

Epinephrine (syn. Adrenaline)

Intramuscular or subcutaneous epinephrine can be life-saving in anaphylaxis and in severe laryngeal angio-oedema but should be used with caution in hypertension and ischaemic heart disease. Dosing is weight-dependent. The British National Formulary (Issue 40) currently recommends 0.5 mL of 1:1,000 [500 micrograms] epinephrine by intramuscular injection for adults and adolescents. Fixed-dose epinephrine pens delivering 300 micrograms for adults or 150 micrograms in children between 15 and 30 kg may be carried by patients for emergency self-administration if the history indicates that the individual is at risk of further life-threatening attacks. If after the first dose of epinephrine there is no significant relief of symptoms, a further dose should be given. Epinephrine is not considered helpful for angio-oedema caused by C1 esterase inhibitor deficiency (III). There is currently no licensed epinephrine aerosol inhaler available in the UK.

Immunosuppressive Therapies

Plasmapheresis and intravenous immunoglobulin may be effective in severe autoimmune chronic urticaria (II-ii). Cyclosporin A has recently been shown to be effective for patients with severe autoimmune urticaria unresponsive to antihistamines (I, A) but only 25% of the responders remained clear or much improved 4 to 5 months later.

Other Interventions

Although some food additives and natural salicylates may aggravate aspirin-sensitive chronic urticaria the value of avoidance is controversial. In one prospective open study of chronic urticaria inpatients, 73% of 64 improved within 2 weeks of a strict pseudoallergen diet but confirmed exacerbations on provocation testing with individual pseudoallergens were only demonstrated in 19% of them (III, B).

Thyroxine treatment of euthyroid patients with chronic idiopathic urticaria and with evidence of thyroid autoimmunity may lead to remission of urticaria (III, C).

Psoralen photochemotherapy, ultraviolet B phototherapy, and relaxation therapies for chronic urticaria have yielded unconvincing results (VI, D).

Although some immediate benefit from using very potent topical steroids under occlusion for chronic urticaria has been reported, the use of topical steroids is not recommended.

Treatment of C1 Esterase Inhibitor Deficiency

Treatment options are summarized in Table 4 of the original guideline document. Maintenance therapy is only necessary for patients with symptomatic recurring angio-oedema or related abdominal pain. Anabolic steroids are the treatment of choice for most patients (III, B). Virilizing side-effects may occur even at the low doses needed for long-term maintenance. Regular monitoring for hepatic inflammation and tumours is essential. Tranexamic acid may be used for maintenance but is contraindicated in patients with a history of thrombosis. Regular eye examinations and liver function tests are recommended by the manufacturer in the long-term treatment of hereditary angio-oedema.

Prophylaxis before planned surgery or dental procedures includes taking tranexamic acid 3 to 4 days beforehand or increasing the dose of established maintenance therapies with tranexamic acid or anabolic steroids. C1 inhibitor concentrate or fresh frozen plasma should be given for emergency treatment of serious angio-oedema attacks or as prophylaxis before emergency surgery, especially when intubation is necessary.

Key Points

1. Urticaria can usually be classified on the clinical presentation without extensive investigation. The weals of physical urticaria usually last less than 1 hour (except delayed pressure urticaria) whereas those of ordinary urticaria typically last from 2 to 24 hours. Urticarial vasculitis should be sought by skin biopsy if weals last longer.
2. Urticaria often remains idiopathic after allergic, infectious, physical, and drug-related causes have been excluded as far as possible. At least 30% of patients with chronic idiopathic disease appear to have an autoimmune aetiology. The autologous serum skin test is a reasonably sensitive and specific marker for histamine releasing autoantibodies in this group.
3. Advice on general measures and information can be helpful for most patients with urticaria. Over 40% of hospital urticaria patients show a good response to antihistamines, which are the mainstay of therapy.
4. Combinations of non-sedating H1 antagonists with other agents, such as H2 antagonists and sedating antihistamines at night can be useful for resistant cases.
5. Oral corticosteroids should be restricted to short courses for severe acute urticaria or angio-oedema affecting the mouth although more prolonged treatment may be necessary for delayed pressure urticaria or urticarial vasculitis.
6. Immunosuppressive therapies for autoimmune urticaria should be restricted to patients with disabling disease who have not responded to optimal conventional treatments.

Definitions:

Levels of Evidence

I: Evidence obtained from at least one properly designed, randomized controlled trial

II-i: Evidence obtained from well designed controlled trials without randomization

II-ii: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

IV: Evidence inadequate owing to problems of methodology (e.g., sample size, or length or comprehensiveness of follow-up or conflicts of evidence)

Grades of Recommendation

A. There is good evidence to support the use of the procedure.
B. There is fair evidence to support the use of the procedure.
C. There is poor evidence to support the use of the procedure.
D. There is fair evidence to support the rejection of the use of the procedure.
E. There is good evidence to support the rejection of the use of the procedure

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

To provide consistent high level care to patients with urticaria and angio-oedema

POTENTIAL HARMS

- Doxepin, hydroxyzine, and chlorpheniramine may cause drowsiness and reduced cognitive function. Doxepin has anticholinergic side effects.
- Anabolic steroids: Virilizing side effects may occur even at the low doses needed for long-term maintenance. Regular monitoring for hepatic inflammation and tumours is essential.
- Tranexamic acid may affect colour vision.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Mizolastine is contraindicated in heart failure and when there is prolongation of the Q-T interval. It should be avoided with drugs that inhibit hepatic metabolism via cytochrome P450 (including macrolide antibiotics and imidazole antifungals) and with drugs that have potential arrhythmic properties (including tricyclic antidepressants, such as doxepin).
- If possible, it is best to avoid all antihistamines in pregnancy, especially during the first trimester, although none have been shown to be teratogenic in humans. Current United Kingdom manufacturers' Data Sheets recommend that cetirizine, loratadine, and mizolastine should be avoided in pregnancy and breast feeding.
- Tranexamic acid is contraindicated in patients with a history of thrombosis.

QUALIFYING STATEMENTS

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- These guidelines, prepared on behalf of the British Association of Dermatologists, reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligent.
- It is important that these guidelines are used appropriately in that they can only assist the practitioner and cannot be used to mandate, authorise, or outlaw treatment options. Of course it is the responsibility of the practising clinician to interpret the application of guidelines, taking into account local circumstances.
- Guidelines are inherently a fluid, dynamic process and will be updated on the British Association of Dermatologists (BAD) Web site on a regular basis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Audit Points

1. The value of laboratory investigations not indicated by the history
2. Additional clinical benefit from exceeding the licensed dose of antihistamines
3. The outcome of unlicensed therapies and other interventions (including diet) for the treatment of urticaria

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. Br J Dermatol 2001 Apr;144(4):708-14. [27 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Apr

GUIDELINE DEVELOPER(S)

British Association of Dermatologists

SOURCE(S) OF FUNDING

British Association of Dermatologists

GUIDELINE COMMITTEE

British Association of Dermatologists Therapy Guidelines and Audit Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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Committee Members: N H Cox (Chairman); A. Anstey; C. Bunker; M. Goodfield; A. Highet; D. Mehta; R. Meyrick Thomas; J. Schofield

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Griffiths CE. The British Association of Dermatologists guidelines for the management of skin disease Br J Dermatol. 1999 Sep;141(3):396-7.

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site.

PATIENT RESOURCES

The following is available:

- Urticaria and angioedema. Patient information leaflet. British Association of Dermatologists. Electronic copies: Available from the British Association of Dermatologists (BAD) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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